Interview with Dr. Geoffrey Cox of PIC Solution Inc.

Current trends in SFC and Chiral Chromatography

Dr Geoffrey Cox was educated at the University of Sheffield, England, being awarded the degree of PhD in organic chemistry. Since then his career has been centered around chromatography, starting with preparative gas chromatography through introduction of HPLC to the premier Government analytical laboratory in the UK, development of bonded stationary phases and moving to preparative and industrial scale chromatography first with Du Pont and then in the mid-1980s as Director R&D with Prochrom. In 1997 he moved to Chiral Technologies, first in Europe before relocating to the USA as VP Technology, working in chiral separations. In March 2011 he started the US subsidiary of PIC Solution, the French SFC manufacturer, in order to expand the company's business into North America.

Phenomenex:
Do you see SFC (Supercritical Fluid Chromatography)work increasing next year? Five years? Will SFC complement other purification techniques; particularly HPLC, or will it begin to replace it?

Dr. Cox:
At present, packed column SFC is closely tied to the pharmaceutical industry and like many other such techniques will probably grow at around the same rate as the pharmaceutical R&D budget. As people migrate from the big pharma companies to smaller start-ups during this extended period of reorganization I'd expect to see the implementation of SFC spreading also – not only to smaller US companies but also to companies in other countries as products and processes are outsourced. Of course, over the next few years the pharmaceutical companies will be looking for more products; these may well come from the smaller companies rather than from the big pharma R&D groups so we can expect some growth in both sectors. I don't think that SFC will replace HPLC except in a few specific areas. By far the most used technique in HPLC is reversed phase chromatography whereas SFC is a normal phase technique. Many applications won't make the transition; nor, for that matter, will some of the chromatographers! SFC has advantages of speed over HPLC and in some cases this can matter although one can imagine that sooner or later the separations will be so fast that no-one will be able to keep up with the data or sample preparation. But that is a quite different discussion.

Phenomenex:
What is the biggest challenge that SFC needs to overcome to make it a more widely used technique?

Dr. Cox:
I think that the biggest challenge is to develop the "universal" separation method. In HPLC one can use a C18 column with a generic buffer – acetonitrile gradient which will give some sort of separation in the majority of cases. While SFC can employ a wider variety of columns and mobile phase systems for the chromatographer to choose from, it does not have the convenience of a universal (or close to universal) methodology as does HPLC. Conditions suitable for the separation of biomolecules would be a huge help in extending SFC beyond its current, small molecule, application range.

Phenomenex:
Today, SFC is primarily used in lab and small scale settings. Do you think the technology will become more utilized in production scale?

Dr. Cox:
SFC is used in production in one or two industries, most notably in the purification of the omega-3 fatty acid esters from fish oils. It would be very exciting to see the technique extended to other processes. SFC needs the "killer" application, one where the product is so important or the alternative methods are so disadvantageous, for it to move into production scale. At present, the capital investment cost of installing high performance chromatographic systems in production areas seems to be restricting uptake of any chromatographic process at the large scale. There may be some place for SFC at the pilot or small scale preparative purification of costly small molecules as current lab methods could grow into larger scale. Of course, at the large scale production end, SFC has to compete with other techniques such as SMB which are probably more accepted within the engineering community.

Phenomenex:
What applications benefit the most from the advantages of SFC?

Dr. Cox:
SFC is currently ideally suitable for small molecule separations. Probably the majority of preparative scale SFC is carried out to resolve enantiomers of potential new drug products. Here the speed of the separations makes for fast method development and rapid purification. The fact that the main mobile phase component is a gas under ambient conditions makes product recovery both fast and simple. There is increasing use of SFC in purification of synthetic mixtures achirally in very early discovery, replacing the high throughput purifications by HPLC, again because it can be four or five times faster and the products are more concentrated.

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Phenomenex:
Compared to RPHPLC there are relatively few CSPs available for commercial scale purifications. Do the currently available CSPs satisfy the customer's needs in terms of variety?

Dr. Cox:
If we look at the chiral stationary phases currently available, one can usually find one that will allow the analytical separation for the small scale (less than 1g) purification of enantiomers. As the scale of the operation increases, one needs higher selectivity to achieve a given separation which means that there is always some room for the introduction of new phases, even though any given new phase may not facilitate more than a handful of applications. When one considers commercial scale purifications, one is looking for selectivity values close to or exceeding 2 in order to attain sufficient production rate to make the chromatographic process competitive – or even just viable.

If you look at achiral phases, there are some relatively recent developments which extend the range of application and the available selectivity. There is probably some room for more development in this area, even for the smaller scale separations.

On the general subject of commercial scale phases, it is always difficult to determine which one will be useful for any given application and there are arguments for having a range of phases available at the small scale with the potential to develop whichever one turns out to be best for a separation. Of course, that entails a considerable investment in plant by the packing material manufacturer to run the larger scale synthesis of the phase without having too much guarantee that it will ever be used.

Phenomenex:
What improvement do you hope to see in the SFC separations industry in the near future?

Dr. Cox:
The most needed improvements are an extension of the range of phases, both chiral and achiral, that allow more preparative separations to be run at larger scale and the development of new application areas or techniques that allow the "difficult" molecules to be separated under both analytical and preparative conditions. As an example of the latter I am thinking of the introduction of the use of sulfonic acids as additives which have allowed the chromatography of many strongly basic compounds under SFC conditions which simply did not elute – or which only eluted as broad blobs of peaks from the columns. Something that would enable elution of larger peptides & small proteins would certainly be a welcome extension to the application range.

Phenomenex:
Why is the idea of "Green Chemistry" so important today?

Dr. Cox:
On a very general level, look at the world as it is right now and the way that climate change appears to be taking us. We ought to be trying to leave the world in at least the state in which we found it, allowing our children and their children to enjoy life much as we do. An analytical HPLC which runs 24/7 for a year will produce around 3.5 tons of waste solvent, all of which is generally burned. It is not difficult to extrapolate that to all the HPLC systems, analytical and preparative and end up with a huge amount of greenhouse gases liberated from the activities just of chromatographers. Switching to SFC will reduce that amount, especially as most of the CO2 that is used for chromatography is generated by other processes and would otherwise just be liberated into the atmosphere.

The other very interesting aspect of preparative SFC is that it is easy to recycle the CO2, recirculating more than 90% of that used in the process. This is much more difficult and expensive to do with organic solvents which need to be distilled and which still can entrain products through the recovery process. Of course, one should not just stop the "greening" process at chromatography, but as chromatographers we can – and must – start somewhere.